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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO.
08/807,506	02/27/97	SMIT	2362-17B0410

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EXAMINER	
BUDENS, R	
ART UNIT	**PAPER NUMBER**
1648	6

DATE MAILED: 03/12/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 54-83 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 54-56, 66-68, 78 is/are rejected.
☒ Claim(s) 57-65, 69-77, 79-83 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☒ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

The Art Unit location of your application in the Patent and Trademark Office has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1648.

Applicant is encouraged to file an information disclosure statement including (1) a form PTO-1449, "Information Disclosure Citation" listing patents, publications and other information material to the instant application; (2) a concise explanation of the relevance of each listed item; (3) a copy of each listed item; and (4) a disclosure of related co-pending applications. See 37 C.F.R. §§ 1.97-1.98.

The following informality has been noted and requires correction in response to this Office Action. The attached form PTO 948 indicates that "Figures must Be Numbered Separately", i.e. "Figure 1A," "Figure 1B," etc. (see Item 7 and 37 CFR 1.84(i and j). **While submission of formal drawings can be held in abeyance until such time as allowable subject matter is determined, Applicant is required to amend the Brief Description of the Drawings, if necessary, in response to this Office Action to properly reflect the required corrections of the Drawings.**

The Examiner acknowledges Applicant's Preliminary Amendment, Paper No. 3, filed February 27, 1997. In view of Applicant's Preliminary Amendment, the status of the claims is as follows: Claims 1-53 have been canceled; Claims 54-83 are currently pending before the Examiner.

Claims 57-65, 69-77 and 79-83 are objected to under 37 C.F.R. 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See M.P.E.P. 608.01(n). Accordingly, the claims have not been further treated on the merits and this Office Action is directed only to

the examination of claims 54-56, 66-68 and 78.

Claims 54-56, 66-68 and 78 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 55-56 and 68 are vague and indefinite in that the claims depend from canceled claims. Amendment of claims 55-56 and 68 to recite the appropriate dependency or, alternatively, to incorporate all of the limitations of the canceled claims would obviate this rejection. For the purposes of examination, the Examiner has presumed that Applicant's intent was to have claims 55-56 depend from newly added claim 54 and, likewise, to have claim 68 depend from claim 67 and the claims have been examined accordingly. Claims 54-56, 66-68 and 78 are vague and indefinite in the recitation "and/or" since it is unclear precisely what is being claimed. Amendment of claims 54-56, 66-68 and 78 to delete "and" or "or" would obviate this rejection. Claim 54 is further vague and indefinite in the recitation "peptide hormones or protein hormones..." since claim 54 constitutes an improper Markush claim. Amendment of claim 54 to recite "and" would obviate this rejection. Claim 54 is further vague and indefinite in the recitation "selected from the cytokine super family" since it is unclear whether Applicant is referring to IL2-IL-7 or additional members of the cytokine super family. Amendment of claim 54 to delete "selected from the cytokine super family" would obviate this rejection. Claim 56 is further vague and indefinite in the recitation "for example" since it is unclear whether the claim is being limited to Endo Glu C or Endo Lys C. Amendment of claim 56 to delete "for example" would obviate this rejection. Claims 66-68 are vague and indefinite in the recitation "in close proximity" since it is unclear at what distance the modification can exist and still fall within the metes and bounds of the claims. Amendment of claims 66-68 to delete "or in close proximity" would obviate this rejection. Claim 66 is vague and

indefinite in the recitation "a partial or complete catalytic center" since it is unclear what would constitute a "partial" or a "complete" catalytic center. Amendment of claim 66 to more clearly point out and define the location of the desired modifications would obviate this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claim 78 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 78 is directed to methods of inhibition, suppression and/or cure of HIV infection by any of a number of methods. However, the specification does not provide sufficient evidence to establish that the claimed method would indeed cure HIV. To date, despite extensive research and expense, there is no known cure for HIV. Applicant's specification does not set forth any sufficient teachings to allow one skilled in the art to cure HIV without undue experimentation. Neither has Applicant established that lowering antibody levels by any of the claimed means would necessarily result in inhibition, suppression or cure of HIV. Indeed, one skilled in the art would reasonably conclude that lowering antibody levels in a host would favor the HIV infection rather than suppressing or inhibiting the infection. Nor does the specification establish that lowering **any** antibody level would result in inhibition of HIV infection.

It is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation.

Further, it is well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Further, as taught by Fahey et al. (R), clinical trials using a variety of immunologically based therapies have not yielded successful results in the treatment and/or prevention of HIV infection (see Table 1). Fahey et al. particularly discloses that monoclonal antibody therapies have not provided any clinical benefits and "it is not clear how adding these additional antibodies would make a difference" (see page 3, second column, third full paragraph). The failure of all immune-system-boosting therapies for treating AIDS is further discussed by Fox (S). The teachings of Fahey et al. and Fox are further confirmed by Haynes et al. (T). Haynes et al. teach the major scientific obstacles blocking development of HIV vaccines (see page 40, first column, second full paragraph). Further,

Haynes et al. teach that "Current animal models of either HIV or simian immunodeficiency virus (SIV) fall short of precisely mirroring human HIV infection" and that "lacking these models, researchers must turn towards human clinical trials to answer many of the difficult questions about HIV pathogenesis and HIV vaccine development" (see page 40, first column, third full paragraph). Thus, it is clear from the evidence of Fahey et al., Fox, and Haynes et al. that the ability to treat and/or prevent HIV infection is highly unpredictable and has met with very little success.

Applicants have not provided any convincing evidence that their claimed invention is indeed useful as a therapeutic or preventative for HIV infection and have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention with a reasonable expectation of success and without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

> **A person shall be entitled to a patent unless--**
>
> **(b) the invention was patented or described in a printed publication in this country or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

Claims 66-68 are rejected under 35 U.S.C. § 102(b) as being anticipated by any of Smit et al., *Electrophoresis* 15:251-254, February 1994, Lopez et al., *Proc. Natl. Acad. Sci. USA* 89:11842-11846, December 1992, Lokker et al., *J. Biol. Chem* 266(16):10624-

10631, 5 June 1991, or Shaw, WO 89/05824, all cited on Applicant's International Search Report.

Each of the references teach modifications to proteins and, in particular, to interleukins. Thus, each of the references teach modified signal substances of the claimed invention. Smit et al. teach modifications to IL-3 essentially identical to the claimed invention (see Abstract). Lopez et al. also teach modifications to IL-3 analogous to the teachings of Smit et al. and the claimed invention (see Abstract). Lokker et al. further teach modifications of IL-3 including modification/identification of residues required for biological activity (see Title and Abstract). Shaw teaches modification of polypeptides including the interleukins and growth factors (see pages 3-4). Thus, the references fully discloses to the public that which is claimed in this application and, inasmuch as this disclosure was made more than one year prior to the filing of this patent application, the issuance of a patent is barred.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> **A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**
>
> **Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligations under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 54-56 and 66-68 are rejected under 35 U.S.C. § 103 as being unpatentable over Smit et al., *Electrophoresis* 15:251-254, February 1994, Lopez et al., *Proc. Natl. Acad. Sci. USA* 89:11842-11846, December 1992, Lokker et al., *J. Biol. Chem* 266(16):10624-10631, 5 June 1991, or Shaw, WO 89/05824 as discussed above and further in view of Applicant's admissions in the specification at page 15, lines 1-19).

As stated above, Smit et al., *Electrophoresis* 15:251-254, February 1994, Lopez et al., *Proc. Natl. Acad. Sci. USA* 89:11842-11846, December 1992, Lokker et al., *J. Biol. Chem* 266(16):10624-10631, 5 June 1991, or Shaw, WO 89/05824 all teach well known and routinely used methods of producing modified proteins having altered biological activity. None of the references teach further characterization of the modified peptides using protein fragmentation with Endo Glu C and Endo Lys C or mass spectrometry. However, these methods are all well known in the art as evidenced by the teachings of Applicant's own specification establishing that these reagents and methods were well known and commercially available to one of ordinary skill in the art at the time the claimed invention was made. Therefore, absent convincing objective evidence to the contrary, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify proteins according to the well known methods of any of Smit et al., *Electrophoresis* 15:251-254, February 1994, Lopez et al., *Proc. Natl. Acad. Sci. USA* 89:11842-11846, December

1992, Lokker et al., *J. Biol. Chem* 266(16):10624-10631, 5 June 1991, or Shaw, WO 89/05824 for the purpose of identifying and modifying the biological activity of the protein and it would have been obvious to further characterize the modified protein using protein fragmentation and mass spectrometry since these methods for characterizing proteins were well known in the art. One of ordinary skill in the art would have been motivated to modify the proteins in order to enhance biological activity as evidenced by the numerous prior art references cited above and would have been motivated to further characterize the modified proteins so as to determine the optimal modifications for enhanced biological activity. One would have had a reasonable expectation of success since modifications to proteins were already well known in the art and since methods of characterizing modifications using such methods as Endo Glu C and Endo Lys C and mass spectrometry were well known and commercially available in the art.

Claim 78 is rejected under 35 U.S.C. § 103 as being unpatentable over Robinson et al., *The Lancet*, April 9, 1988 (U). Robinson et al. disclose the presence of HIV enhancing antibodies in sera of HIV infected patients (see Summary). Robinson et al. does not specifically teach removal of the antibodies. However, the level of ordinary skill in the HIV art is exceptionally high and, absent convincing objective evidence to the contrary, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the well known methods of plasmapheresis to remove the enhancing antibodies according to Robinson et al. for the expected benefit of increasing the patient's ability to resist HIV infection. One would have been motivated by the long felt need for improved therapies for HIV infection and would have had a reasonable expectation of success since methods of removing antibodies by plasmapheresis were well known in the art at the time the claimed invention was made.

No claim is allowed.

Papers relating to this application may be submitted to Group 1600 by facsimile transmission. The Fax number is (703) 308-4242. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Robert D. Budens at (703) 308-2960. The Examiner can normally be reached Monday-Thursday from 6:30 AM-4:00 PM, (EST). The Examiner can also be reached on alternate Fridays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Don Adams, can be reached at (703) 308-0570.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at (703) 308-0196.

Robert D. Budens
Primary Examiner
Art Unit 1648

rdb
March 7, 1998